



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶:A61K 38/17, C12N 5/10, G01N 33/50,
C07K 16/18

A1

(11) International Publication Number:

WO 98/47525

(43) International Publication Date:

29 October 1998 (29.10.98)

(21) International Application Number: PCT/GB98/01144

(22) International Filing Date: 20 April 1998 (20.04.98)

(30) Priority Data:

9708092.3

22 April 1997 (22.04.97)

GB

(71) Applicant (for all designated States except US): UNIVERSITY
OF DUNDEE [GB/GB]; Dundee DD1 4HN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): LANE, David, Philip
[GB/GB]; Magicwell House, Balmullo, St. Andrews, Fife
KY16 08N (GB).(74) Agents: KIDDLE, Simon et al.; Mewburn Ellis, York House,
23 Kingsway, London WC2B 6HP (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE,
GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO
patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,
IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

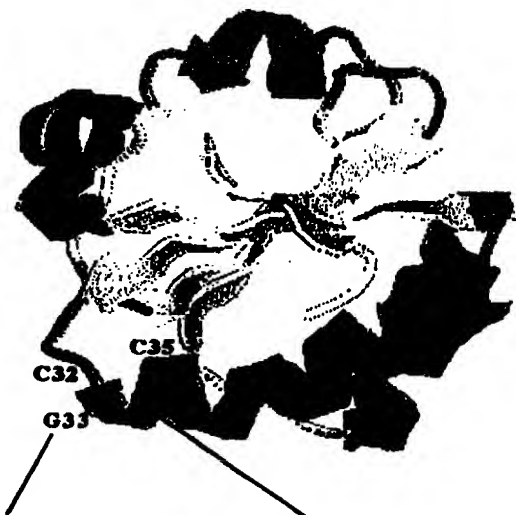
With international search report.

Before the expiration of the time limit for amending the
claims and to be republished in the event of the receipt of
amendments.

(54) Title: MATERIALS AND METHODS RELATING TO INHIBITING THE INTERACTION OF p53 AND mdm2

(57) Abstract

Mdm2 binds to p53 in cells in which mdm2 is not overexpressed, i.e. in cells in which mdm2 is expressed at normal or low levels, and that in these cells, this interaction targets the p53 for degradation. This finding means that inhibiting mdm2 production and/or inhibiting the binding of mdm2 to p53 allows levels of p53 to increase by reducing the clearance of p53 by mdm2, and can be used to activate p53 function in cells other than those in which mdm2 is overexpressed. This allows the use of an agent having the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 in a population of cells, in the preparation of a medicament for activating p53, wherein the population of cells do not overexpress mdm2. Such medicaments are useful in the treatment of conditions such as cancer, viral infections or conditions in which p53 or mdm2 is not functional.



TIP

TIP 12/1

PPLSQETTFSDLWKLIPENG

PPLSMPRMDYHEGLNENG

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

Int. Application No.
PCT/GB 98/01144

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/17 C12N5/10 G01N33/50 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 20238 A (UNIV JOHNS HOPKINS) 14 October 1993 cited in the application see page 7, paragraph 5 see page 10, paragraph 3 - page 12, paragraph 1	1-11
X	WO 96 02642 A (UNIV DUNDEE ; PICKSLEY STEVEN MICHAEL (GB); LANE DAVID PHILIP (GB)) 1 February 1996 cited in the application see page 1, paragraph 1 see page 3, paragraph 2 - page 6, paragraph 2	1-11
	--- -/-- ---	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

20 August 1998

Date of mailing of the international search report

01/09/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Sitch, W

INTERNATIONAL SEARCH REPORT

Int Application No
PCT/GB 98/01144

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BLAYDES ET AL: "TOLERANCE OF HIGH LEVELS OF WILD-TYPE P53 IN TRANSFORMED EPITHELIAL CELLS DEPENDENT ON AUTO-REGULATION BY MDM-2" ONCOGENE, vol. 14, no. 15, 17 April 1997, pages 1859-1868, XP002075048 cited in the application see page 1859 see abstract see page 1866, paragraph 3</p>	1-11
X	<p>BÖTTGER ET AL: "IDENTIFICATION OF NOVEL MDM2 BINDING PEPTIDES BY PHAGE DISPLAY" ONCOGENE, vol. 13, 1996, pages 2141-2147, XP002075049 cited in the application see the whole document</p>	1-11
A	<p>DATABASE MEDLINE FILE SERVER STN KARLSRUHE ABSTRACT 93390942, KOVAR ET AL: "NARROW SPECTRUM OF INFREQUENT P53 MUTATIONS AND ABSENCE OF MDM2 AMPLIFICATION IN EWING TUMOURS" XP002075050 see abstract & ONCOGENE, vol. 8, no. 10, October 1993, pages 2683-2690,</p>	
P, X	<p>WO 98 01467 A (CIBA GEIGY AG ;CANCER RES CAMPAIGN TECH (GB); LANE DAVID (GB); BOE) 15 January 1998 see the whole document see page 11, paragraph 4 - paragraph 5 see page 16, paragraph 2 - page 17, paragraph 1</p>	1-28

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/01144

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12-21 partially, insofar as they concern in vivo methods, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01144

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320238 A	14-10-1993	US 5411860 A	02-05-1995
		AT 159985 T	15-11-1997
		AU 681851 B	11-09-1997
		AU 4278893 A	08-11-1993
		CA 2133306 A	14-10-1993
		DE 69315068 D	11-12-1997
		DE 69315068 T	09-04-1998
		DK 635068 T	20-04-1998
		EP 0635068 A	25-01-1995
		ES 2110608 T	16-02-1998
		JP 7505294 T	15-06-1995
		US 5420263 A	30-05-1995
		US 5550023 A	27-08-1996
		US 5519118 A	21-05-1996
		US 5618921 A	08-04-1997
		US 5756455 A	26-05-1998
		US 5708136 A	13-01-1998
		US 5736338 A	07-04-1998
		US 5606044 A	25-02-1997
		US 5702903 A	30-12-1997
WO 9602642 A	01-02-1996	US 5702908 A	30-12-1997
		US 5770377 A	23-06-1998
		AU 684194 B	04-12-1997
		AU 2987695 A	16-02-1996
		CA 2195533 A	01-02-1996
		EP 0773996 A	21-05-1997
WO 9801467 A	15-01-1998	JP 10506525 T	30-06-1998
		AU 3847997 A	02-02-1998